

THE INFLUENCE OF FOOD INTAKE ON THE EFFECT OF TWO CONTROLLED RELEASE FORMULATIONS OF FUROSEMIDE

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ABSTRACT

Differences in the urinary excretion rate of furosemide may explain discrepancies observed between the bioavailability and the total diuretic effect of different formulations of this drug. Furosemide was given at a dose of 60 mg as two oral controlled release (CR) formulations (FR and LR), with and without breakfast, in a randomized, four-treatment, four-period, crossover design to 28 healthy volunteers. Urinary volume, and contents of furosemide and sodium, were measured in samples taken over 24 h. The extent and rate of absorption of furosemide from FR were decreased after breakfast as compared to fasting: the mean (SD) of total furosemide excreted decreased from 11.38 (3.12) to 7.73 (1.67) mg, $p < 0.0001$, and the median (range) mean residence time increased from 6.3 (4.1–9.3) to 9.5 (5.9–11.8) h, $p < 0.001$. On the other hand, the extent of absorption of LR was increased after breakfast, from 8.04 (3.32) to 9.45 (1.83) mg, $p < 0.05$, without a significant change in MRT. FR had a higher extent and rate of absorption than LR during fasting, but its extent of absorption was lower than that of LR in the postprandial state. Interestingly, the total fraction of furosemide absorbed, as estimated from total furosemide excretion, was not correlated with the total diuresis ($r^2 = 0.079$) and the differences in drug response compared among the four periods were much smaller than would be expected from the differences in amount absorbed. This discrepancy may be explained by differences in urinary excretion rate of furosemide and, related to this, differences in efficiency profiles between the four treatments. Therefore, the urinary excretion profile of a formulation of furosemide may be more important for the cumulated drug effect than the amount absorbed.

KEY WORDS: furosemide; controlled release; pharmacokinetics; pharmacodynamics; food

INTRODUCTION

Loop diuretics are considered to act from the endotubular side of the nephron.¹⁻³ Therefore, the pharmacological response to furosemide, i.e. diuresis or natriuresis, is adequately described by the sigmoid E_{\max} model,

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where effect is expressed as a function of the urinary excretion rate of the drug.⁴

In addition to this classical approach, another pharmacodynamic parameter, which is effect per concentration, can be expressed as a function of concentration and the parameters of the sigmoid E_{\max} model. This variable is called efficiency, to distinguish it from effect.⁵ In the case of furosemide, efficiency gives an estimate of how much effect is obtained per unit of stimulus (for example millilitres per milligram) through the range of drug urinary excretion rate.⁵⁻⁷ Since a maximum effect (E_{\max}) is observed with furosemide, efficiency decreases at high excretion rates. Efficiency is also characterized by a maximum at a certain furosemide excretion rate that can be calculated from the parameters of the E_{\max} model if the slope factor $S > 1$.⁷ The efficiency concept has been used to explain that the time course of drug delivery is an important factor for the cumulated pharmacological effect.⁵⁻⁸

Furosemide is subject to absorption limited kinetics, which means that its rate of absorption limits the rate of excretion of the drug in urine.⁹ Since food may affect both rate and extent of drug absorption, the present study was performed to assess the effect of food on bioavailability, effect, and efficiency of two controlled release (CR) furosemide formulations.

METHODS

Subjects and study design

Twenty-eight healthy Caucasian subjects participated in the study after giving informed consent and after approval had been obtained from an ethics committee. There were 19 males and 9 females. Their ages ranged from 20 to 37 years and their body weights from 51 to 92 kg.

The study was an open, randomized, four-treatment, four-period, crossover design. It was part of a bioequivalence study comparing a test drug, Furix Retard® (FR), Benzon Pharma, and a reference drug, Lasix Retard® (LR), Hoechst. Each subject received 60 mg of furosemide as a single oral dose of each of the two formulations, with and without food, with a washout period of one week. The sessions were as follows: FR without (treatment A) and with breakfast (treatment B) and LR without (treatment C) and with breakfast (treatment D). All doses were 60 mg but an assay of batch content was performed and deviations (0.2 and 5.8%, respectively) were adjusted for.

On the morning of each study session, after overnight fasting, each subject emptied his/her bladder and had the tablet given with 300 mL of water. A balanced solution of carbohydrates and electrolytes was used for isovolumetric oral replacement of voided volumes. The solution contained per litre 75 g of carbohydrates, including 54 g of monosaccharides and disaccharides, 12.61 mmol Na⁺, 2.05 mmol K⁺ and 7.32 mmol Cl⁻ and had an energy

value of 1650 kJ. Food and fluid intake was strictly standardized during the 24 h study periods. During two of the sessions (B and D), the subjects received a high-fat breakfast meal, with a content (bacon, eggs, full fat milk, bread, cheese) according to the US FDA recommendations.¹⁰ The meal, which was taken just before dosing, contained 61 g fat, 58 g carbohydrate and 31 g protein. During the other two sessions (A and C), the subjects were fasting. During all sessions, lunch was served 4 h after dose intake, an afternoon snack after 7 h, dinner after 10 h and finally an evening snack was given after 12 h. The total intake of fluid during meals was 1200 mL (water, decaffeinated coffee, and fruit juice).

Urine samples were obtained by voiding at 2 h intervals during the first 10 h and the last collected portion was from 10 to 24 h after dosage. The volumes were measured and aliquots were frozen at -20°C . Furosemide concentrations were determined by HPLC.¹¹ Sodium was assayed by ion selective electrodes.

Calculations

The sigmoid E_{\max} model, also known as the Hill equation, is expressed as

$$E = \frac{E_{\max} C^s}{C_{50\%}^s + C^s} + E_0 \quad (1)$$

If we select to study volume diuresis, E expresses the diuretic effect in millilitres per minute, E_0 is basal diuresis, E_{\max} is the maximum drug induced diuresis, $C_{50\%}$ is the furosemide excretion rate associated with half maximum induced diuresis, and S is a fitting parameter known as the slope factor.^{12,13} In pharmacodynamic studies, C usually denotes the independent variable concentration but, in the case of furosemide, C represents the urinary drug excretion rate.

Equation (1), which is an expression of pharmacological effect (E), can be transformed to express efficiency (Eff) by dividing both sides by C :⁵

$$\text{Eff} = \frac{E - E_0}{C} = \frac{E_{\max} C^{s-1}}{C_{50\%}^s + C^s} \quad (2)$$

If urinary volume is selected to represent diuretic effect, Eff is expressed in millilitres per milligram. Effect and efficiency will have different shapes when expressed against C as has previously been shown.^{5,7} Mean furosemide excretion rate and mean diuretic efficiency were calculated for each sampling of each treatment period and equation (2) was fitted to the collection of data for visual clarity (Figure 4).

A total or time averaged efficiency can be calculated for the whole effect event⁸ and is given by

$$\text{total Eff} = \frac{\text{total induced diuresis}}{A_e}$$

in which A_e is the total amount of furosemide excreted in 24 h. In the calculations and plots of efficiency, basal diuresis (E_0) was subtracted. Basal urine volume and basal natriuresis were chosen to be 0.5 mL min^{-1} and $0.065 \text{ mmol min}^{-1}$, respectively.¹⁴ Three subjects were excluded from the calculation of total natriuresis efficiency because of a lower total sodium excretion than the pre-determined basal values.¹⁴ Mean residence times (MRT) were calculated from the urinary excretion data.¹⁵ Differences in MRT were used to estimate differences in mean absorption times (MAT), assuming that the active compound of the two preparations had the same mean time for distribution and elimination.

Statistical analysis

Treatment differences were evaluated by analysis of variance (ANOVA). The statistical analyses were based on log transformed data and on the ordinary linear model,¹⁶ utilizing the SAS GLM procedure corresponding to the four-treatment, four-period crossover design used. Due to the nature of the study, carry-over effects were not included in the model. Ninety per cent confidence intervals (CI) were calculated according to Schuirmann.¹⁷ MRT values were compared by Kruskal-Wallis non-parametric ANOVA and the Wilcoxon signed rank test. Results were considered as significant if $p < 0.05$.

Correlations between total furosemide excreted, maximum furosemide excretion rate, MRT, total diuresis, total efficiency for diuresis, total sodium excreted, and total efficiency for natriuresis were studied by linear regression. Correlation was considered as significant if $p < 0.05$ and $r^2 > 0.5$.

RESULTS

The intake of food had a different influence on the absorption characteristics of the two formulations. Their rate of absorption was differently affected: MRT was increased in the postprandial state as compared with fasting after FR (Table 1). In contrast, MRT was not significantly increased when LR was administered with breakfast. Also, the fraction of furosemide absorbed, as estimated by the total amount of furosemide excreted in 24 h, was decreased after breakfast for the FR formulation, whereas food had the opposite effect on LR (Table 1; Figure 1 (a)).

However, the fraction absorbed was of limited value for predicting drug effect, since no correlation was found between total furosemide excretion and total diuresis (Figure 2). Extent of absorption was 32% lower for FR after

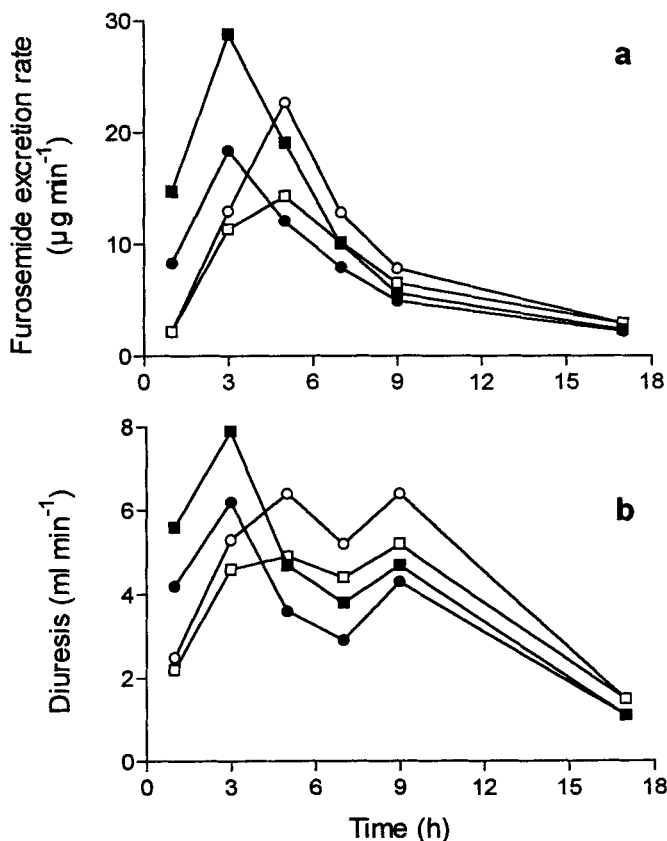


Figure 1. Mean furosemide excretion rate (a) and mean diuresis (b), expressed against the midpoint of each sampling interval, in 28 subjects given FR in the fasting state (■) and together with breakfast (□) and LR in the fasting state (●) and together with breakfast (○)

breakfast when compared to fasting whereas total diuresis was only 7% lower and total natriuresis was virtually the same (Table 1). Table 2 shows the bioequivalence of the total effects for FR. On the other hand, the total diuresis for LR after breakfast was in agreement with the increase in fraction absorbed (27% and 18% higher, respectively). When comparing between the two formulations, the differences in drug response were smaller than the pharmacokinetic differences (Table 1; Figure 1(b)). The formulations were not bioequivalent regarding the total amount of furosemide excreted but their total volume diuresis and natriuresis were hardly different (Table 2).

This discrepancy between extent of absorption and total drug effect (Figure 2) was analysed by a pharmacodynamic approach. The relationship between instantaneous diuresis and furosemide excretion rate is shown in Figure 3. This

Table 1. Urinary excretion data

	FR		LR	
	Fasting	Breakfast	Fasting	Breakfast
Furosemide				
A_e^a (mg)	11.38 (3.12) ^{abc}	7.73 (1.67)	8.04 (3.32) ^b	9.45 (1.83)
max dA_e/dt^d ($\mu\text{g min}^{-1}$)	31 (14) ^{bc}	16 (7) ^c	21 (14) ^b	26 (11)
MRT ^e (h)	6.3 (4.1–9.3) ^{bc}	9.5 (5.9–11.8)	7.7 (3.9–13.3)	8.2 (5.4–12.7)
Volume				
diuresis (mL)	4096 (1281)	3817 (1283) ^c	3436 (1259) ^b	4347 (1374)
total Eff ^f (mL μg^{-1})	0.301 (0.097) ^{bc}	0.417 (0.187)	0.379 (0.226)	0.403 (0.181)
Sodium				
A_e^a (mmol)	207 (72)	206 (60)	184 (86) ^b	215 (55)
total Eff (mmol μg^{-1}) ^{fg}	0.010 (0.006) ^{bc}	0.016 (0.008)	0.013 (0.014)	0.013 (0.005)

^a A_e is amount excreted.

^bStatistically different from food condition.

^cStatistically different from LR.

^dMax dA_e/dt is maximum excretion rate. MRT is mean residence time.

^eResults are given as mean (SD) except for MRT, which is given as median (range).

^fTotal efficiency is adjusted for basal diuresis.

^g $n = 28$ except for sodium total efficiency, for which $n = 25$.

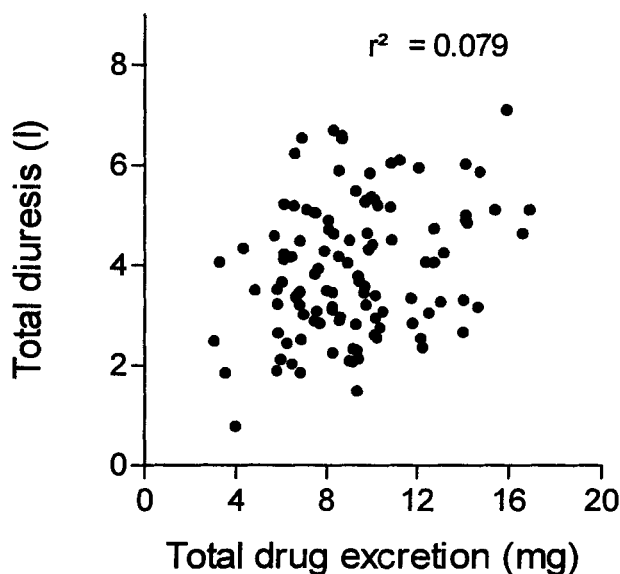


Figure 2. The relationship between total diuretic effect (urine volume) and total amount of furosemide excreted in 28 subjects, during four different treatment periods

Table 2. Treatment ratios as percentages and 90% confidence intervals

	B/A ^a (FR breakfast/ fasting)	D/C ^a (LR breakfast/ fasting)	A/C ^a (FR/LR fasting)	B/D ^a (FR/LR breakfast)
Furosemide				
A_e^b	69 (64–74)	126 (108–146)	140 (126–155)	77 (69–85)
max dA_e/dt^c	54 (48–61)	145 (114–185)	159 (133–189)	59 (50–71)
Diuresis				
volume	93 (81–106)	130 (111–153)	116 (99–135)	82 (71–96)
sodium	102 (89–116)	125 (107–146)	109 (96–124)	89 (79–101)

^aTreatments are A, FR fasting; B, with breakfast; C, LR fasting; D, with breakfast.

^b A_e is amount excreted.

^cMax dA_e/dt is maximum excretion rate.

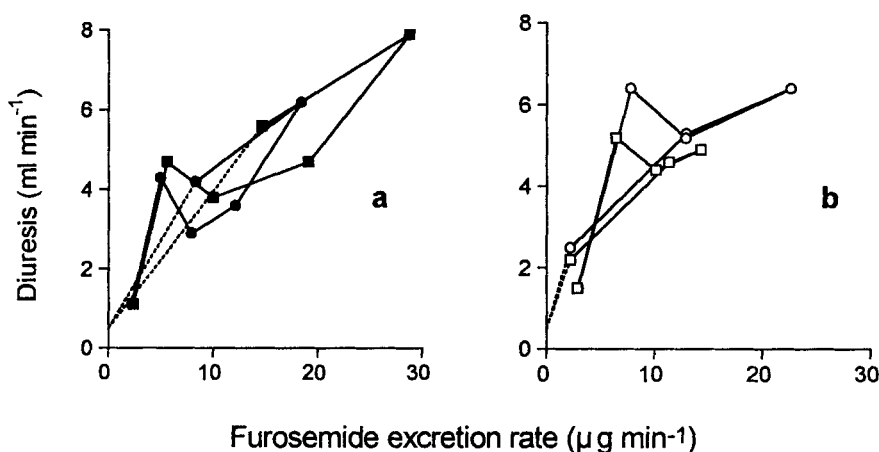


Figure 3. Mean diuresis against mean furosemide urinary excretion rate in 28 subjects given FR (■) and LR (●) in the fasting state (a) and together with breakfast (b, □ and ○, respectively)

relation appears as slightly clockwise hysteresis loops after fasting, which suggests that to some extent tolerance developed during the course of drug action. No hysteresis was observed after breakfast but an unexplained secondary increase in diuresis was apparent between 8 and 10 h, during all four periods (Figures 1 and 3). As shown in previous studies, and as suggested by the modelling of mean results with equation (2), diuretic efficiency was higher at low furosemide excretion rates and there were no major discrepancies between the formulations (Figure 4). Accordingly, there was a consistent relationship between median MRTs, which reflect differences in overall absorption rate, and both mean total volume diuresis and mean total natriuresis efficiencies: FR fasting < LR fasting < LR with breakfast < FR

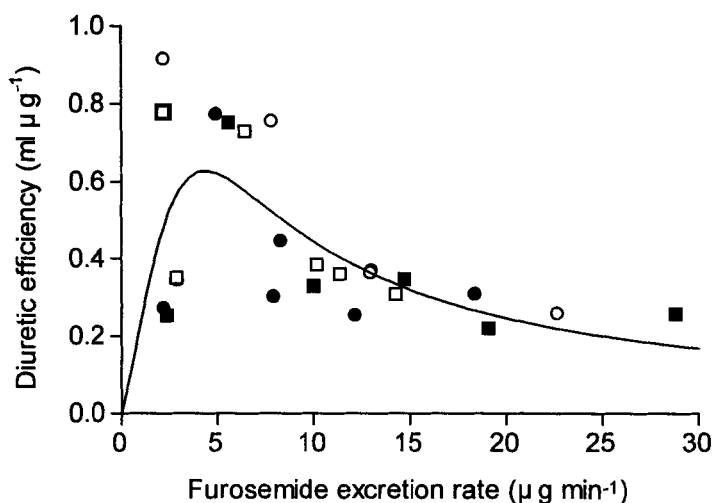


Figure 4. Mean diuretic efficiency (urine volume adjusted for basal diuresis per amount excreted furosemide) against mean furosemide excretion rate in 28 subjects given FR in the fasting state (■) and together with breakfast (□) and LR in the same conditions (● and ○, respectively). The data presented were used to produce a tentative efficiency curve for visual clarity

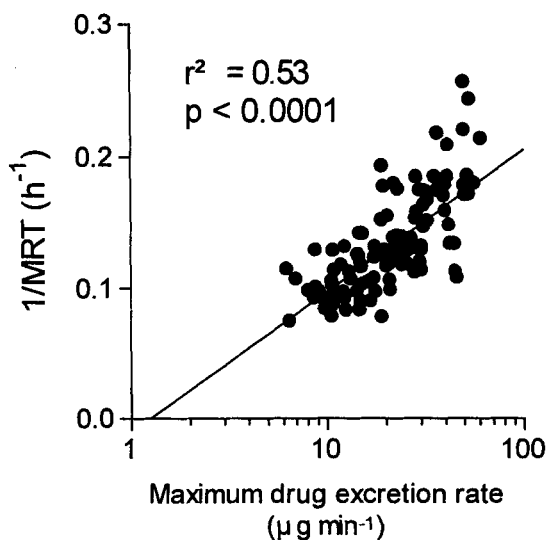


Figure 5. The relationship between mean residence time and maximum furosemide excretion rate in 28 subjects, during four different treatment periods

with breakfast (Table 1). However, no correlation between MRT and efficiencies was observed when analysing individual values.

Both MRT and maximum excretion rate of furosemide are influenced by drug absorption rate. Therefore, a relationship between MRT and maximum

excretion rate could be expected. As shown by Figure 5, MRT was indeed inversely correlated with the logarithm of furosemide maximum excretion rate.

DISCUSSION

Furosemide is subject to absorption limited kinetics, which means that the rate of absorption determines the rate of excretion of the drug in urine.⁹ After food intake, both the fraction of furosemide absorbed and the absorption rate from plain tablets were found to be decreased as compared to the fasting state.⁹ MAT was on average 60 min longer after food intake, which may be explained by delayed stomach emptying with subsequent slower transfer of the drug to the duodenum.⁹ In this study, the difference in MAT between plain tablets and solution was used to calculate the mean *in vivo* dissolution time in the postprandial state. Mean dissolution time was found to be shorter than the MAT for the solution, which may indicate that gastric emptying or transport across the gastrointestinal wall may be more rate limiting for absorption than dissolution.⁹

In our study, fasting and breakfast conditions had opposite effects on the pharmacokinetic parameters of the two CR formulations of furosemide. The exact mechanism behind these different effects is not known. Both formulations are multiple-unit dose systems, i.e. individual coated pellets contained in a capsule. However, there is a difference in the coating material (and technique of coating) of the pellets between the two formulations, giving rise to different *in vitro* release characteristics. The most plausible explanation of the different effects of food may be that the coating material (i.e. the film) is perturbed by food in a different way for the two formulations.

Although both CR formulations obviously gave rise to a response (volume diuresis was more than 6 L in certain subjects), the extent of absorption was not an informative parameter, since it was not correlated with the total diuresis obtained ($r^2=0.079$). Accordingly, differences in drug response were lower than expected with regard to differences in extent of absorption between the two formulations. The fact that the two drugs are bioequivalent for natriuresis may be the more relevant aspect to consider: the main indication of CR furosemide products is the treatment of hypertension, where sodium homeostasis is a major pathophysiologic factor.¹⁸

Because the furosemide excretion rate is influenced by its absorption rate⁹, the time course of drug delivery to its site of action, which is endotubular,¹⁻³ will vary according to dosing conditions. The concept of efficiency,⁵ which gives an estimate of how much effect is obtained per unit of stimulus, has been proposed and applied in furosemide experiments to predict that a slow and constant input of drug into the body would lead to a higher total effect when identical doses are compared.^{6,7,19} This pharmacodynamic parameter is able to explain discrepancies observed between total amount of drug that had reached

the site of action and total effect, during probenecid coadministration,²⁰ with CR drugs,²¹ and in patients with cystic fibrosis.²² The validity of the efficiency concept was confirmed in a study comparing two CR formulations and a plain tablet:⁸ although a markedly (45%) lower total amount of furosemide excreted was observed after CR formulations as compared with plain tablets, total diuresis over 24 h was only 23.5% lower. The efficiency concept was also applied in studies using a continuous infusion in healthy subjects²³ and in patients with chronic renal insufficiency.²⁴

The discrepancy between pharmacokinetics and drug response observed in the present study, which resulted in different total efficiencies, is probably due to differences in input profiles, leading to differences in drug excretion rate. If only pharmacokinetics were considered, the two CR formulations would not be bioequivalent, because of different extents and rates of absorption. However, they may be considered as bioequivalent if total drug response is favoured as the criterion.

As previously reported, drug effect is highly dependent on bioavailability, as defined by both extent and rate of absorption.^{8,11} The concept of efficiency helps in understanding the impact of absorption rate, which defines the time during which the drug is present at its site of action with the highest efficiency.

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APPENDIX

The tentative linear relationship shown in figure 5, between 1/MRT and the logarithm of maximum excretion rate of furosemide, can be deduced as follows, assuming that furosemide kinetics can be simplified to a one-compartment model with first-order absorption (k_a) and first-order elimination (k_e). The maximum furosemide excretion rate is proportional to the maximum plasma concentration (C_{\max}) which in turn can be expressed as a function of t_{\max} ,²⁵ the time at which maximum plasma concentration occurs in a one-compartment model:

$$C_{\max} = Ae^{-k_e t_{\max}} \quad (\text{A1})$$

$$\log C_{\max} = \log A - k_e t_{\max} \quad (\text{A2})$$

However, t_{\max} is a function only of absorption and elimination rate constants:²⁵

$$t_{\max} = (1/(k_a - k_e)) \log(k_a/k_e) \quad (\text{A3})$$

If we assume k_e to be constant, t_{\max} is mostly influenced by the factor $1/(k_a - k_e)$ and will vary in relation to k_a . Assuming an MRT_{IV} (which is $\text{MRT} - \text{MAT}$) of 50 min,⁹ it would in our study be 4–16 times smaller than MRT (Table 1). Therefore, MRT may be used to estimate MAT and consequently, $1/\text{MRT}$ will be well correlated with $1/\text{MAT}$, which is equal to k_a . Now, $\log C_{\max}$ can be found to vary linearly with t_{\max} (A2), which in turn is highly dependent on the variation of k_a . Thus, both $1/\text{MRT}$ and $\log C_{\max}$ will, to a significant degree, be dependent on k_a and the relationship between these two parameters can be expected to be approximately linear as illustrated by figure 5.

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